

A CENTURY OF SAVING LIVES MILLIONS AT A TIME

> JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH



Katya Tsaioun, Ph.D.

## **Presentation Outline**

- About EBTC and its projects
- Why systematic review of literature for safety test methods assessment?
- Examples of EBTC SRs in toxicology:
  - Zebrafish embryotixicity test SR
  - Tox21 SR
- Challenges
- The future: text mining and AI





## EBTC -vision and mission

#### What is EBTC?

EBTC is an international collaboration of science, regulatory and industry leaders that is formed to establish and coordinate evidence-based, transparent toxicology and safety assessment methods to improve the risk assessment standards for regulatory decision making.

#### EBTC's Vision:

Evidence-based toxicology is the standard used to ensure public health, a healthy environment and a sustainable future.

#### EBTC's Mission:

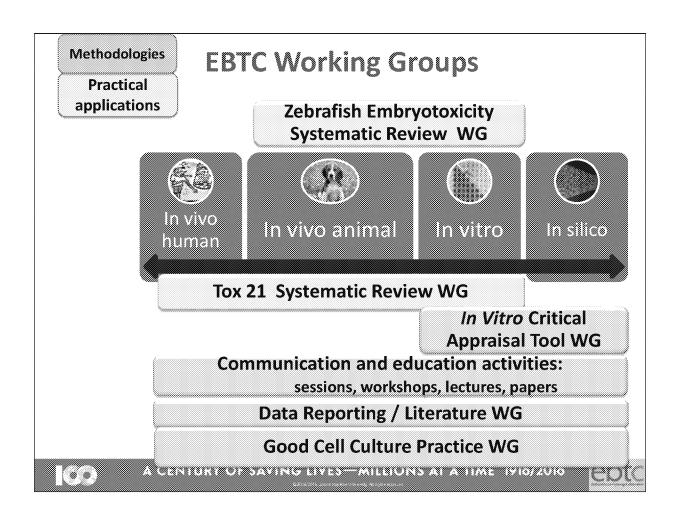
Bring together the international toxicology community to facilitate use of evidence-based toxicology to inform regulatory, environmental and public health decisions.

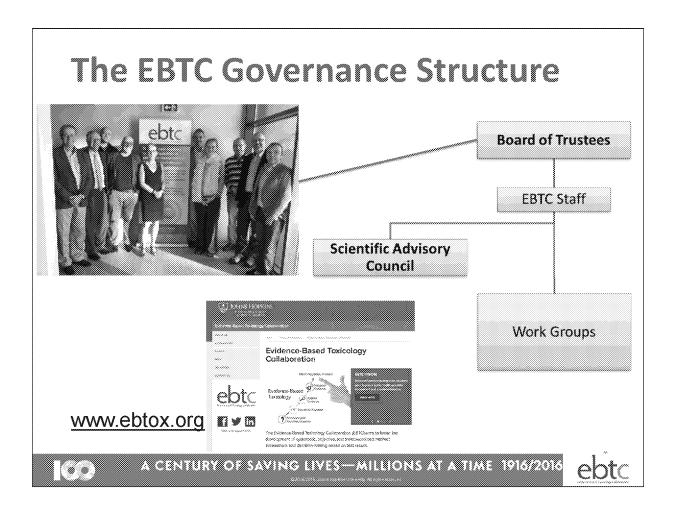
#### **EBTC Funding:**

JHBSHP, Safer Medicines Trust and Beagle Freedom Prize

#### Where is EBTC?

JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH





### **Board of Trustees**



American

Chemistry Council

John R. "Jack" Fowle III formerly at the US EPA; Consultant, Science To Inform,

LLC (President of the Board)

Gerry Kenna Safer Medciines, Trust, UK Suzanne Fitzpatrick Senior Toxicology Advisor, US FDA

**Thomas Hartung** Chair, Evidence-Based Toxicology, Johns Hopkins

University, Director of Center of Alternatives to Ani

**Testing** 

**Kris Thayer** Director, IRIS, US EPA

James FreemanDistinguished Toxicology Associate, ExxonMobilEmily SenaCAMARADES, University of Edinburg, UK

**Didier Verloo** Head of the Assessment and Methodological Support

Unit, European Food safety Agency

Sebastian HoffmannEBTC staff (non-voting member)Rob deVriesSYRCLE (non-voting member)

Martin StephensJohns Hopkins University (EBTC staff) (non-voting member)Katya TsaiounJohns Hopkins University (EBTC staff) (non-voting member)





# Composition EBTC SAC

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1	Fran Kruszewski	ACI	USA	I
2	Manoj Lalu	OHRI	Can	Α
3	Julie Goodman	Gradient	USA	C
4	Vince Cogliano	EPA	USA	G
5	Carl Westmoreland	Unilever	UK	I
6	Malcolm Macleod	CAMARADES	EU	Α
7	Richard Judson	EPA	USA	G
8	Rodger Curren	IIVS	USA	N
9	Daniele Wikoff	ToxStrategies	USA	С
10	Joanna Rochester	TDEX	USA	N
11	Mariska Leeflang	Bond university, Amsterdam	EU	A
12	Miranda Langendam	GRADE	EU	A
13	Robert Wright	JHU	USA	A
14	Barry Hardy	Douglas Connect / OpenTox	EU	N
15	Alan Boobis	Imperial College	EU	Α
16	Annette Kopp-Schneider	Cancer Research Centre	EU	А
17	Hubert Dirven	Public health institute Norway	EU	G
18	Paul Whaley	Lancaster University	EU	Α
19	Simin N. Meydani	Tufts University / USDA	USA	A/G
20	Elisa Aiassa	EFSA	EU	G
21	lan Kimber	University of Manchester	EU	Α



Rob de Vries, SYRCLE SAC Chair

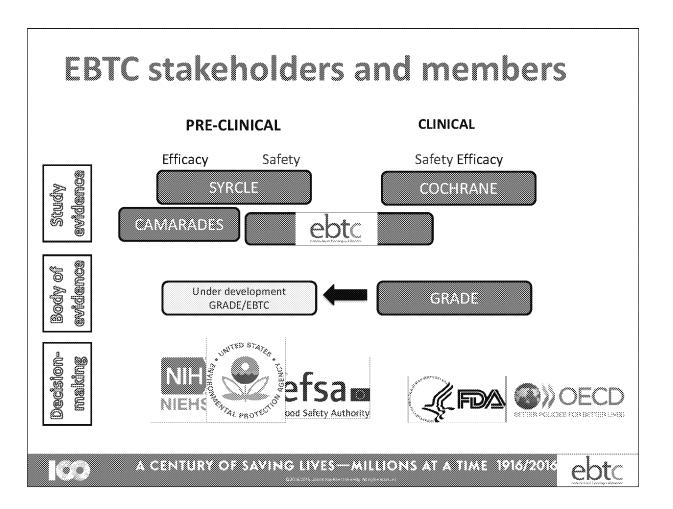


Daniele Wikoff, Tox Strategies SAC Vice-Chair

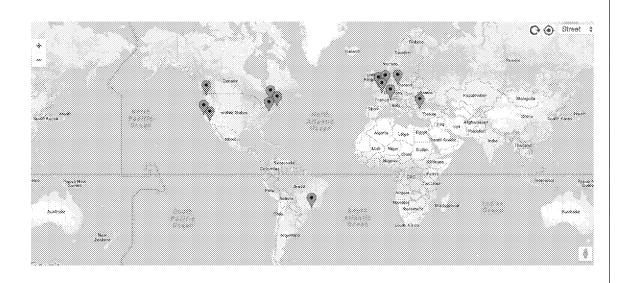
New member: Anne Gourmelon







# EBTC network of stakeholders





## History of evidence-based methodology

#### Origin:

- Clinical trials in medicine
- Organized and developed by Cochrane Collaboration: www.cochrane.org

#### Field of Application:

- Compare medical treatments

### Major principles:

- Transparency
- Consistency
- Statistical rigor
- Minimization of risk of bias that impacts study quality
- Systematic step-wise approach

#### Main instrument:

– Systematic review – why?

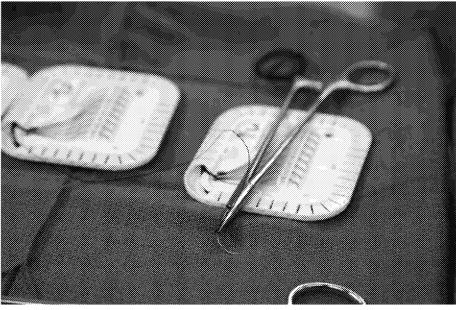




### It's Hard for Doctors to Unlearn Things. That's Costly for All of Us.

Procedures live on even after they've been proved ineffective. It can lead to harms and wasted resources.

It took 30 years

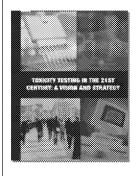


out

btc

Part of a doctor's tool kit is learning new things, but also unlearning some things. The second part may be harder than the first. Her Wissen/The New York Times

# Test validation and EBT – a logical connection



Limitations of current validation approaches:

- Time- and resource-consuming
- Non-comprehensive
- Focus on prediction of status quo test (not relevant to main question)

Advantages of EBT approach:

- Using historical published data
- Rely on proven EBM framework
- Can focus on mechanistic relevance







## Bottleneck: Validation

- Legal underlying reasons for regulatory testing
  - High legal barriers for changing regulatory requirements
- Many agency stakeholders are involved
- Different requirements in different countries
  - Harmonization is needed
- Current validation efforts are focused on precision
  - Need focus on species relevance

Can evidence-based methods provided the needed evidence?



How can SR assist in test validation? Proof-of-principle.

A CENTURY OF SAVING LIVES—MILLIONS AT A TIME 1916/2016

# **PECO** question

- population

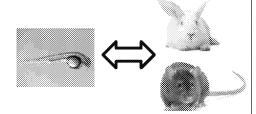
E - exposure

C - comparator / control

outcomes



# Question PICO



Index Test

What is the performance of the Zebrafish Embryo Test (ZET) in

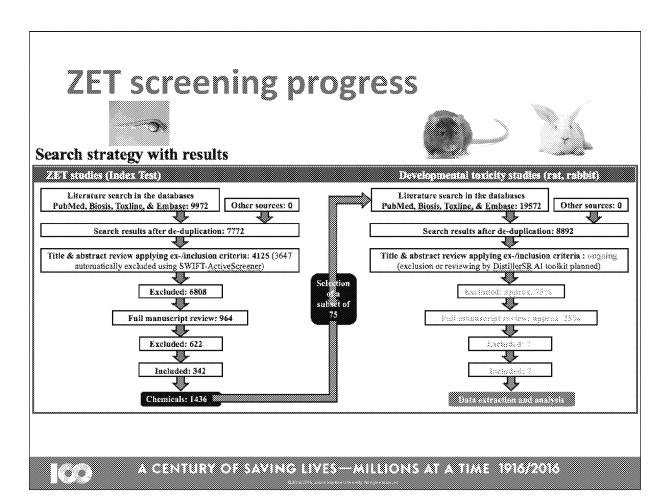
Outcome

predicting the presence and absence of malformations in guidelines studies of prenatal development toxicity in rats and rabbits (OECD TG 414 and equivalents)?

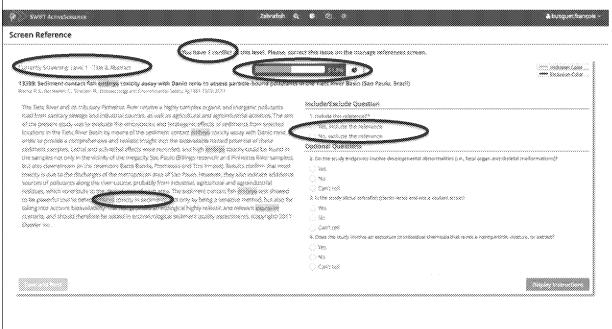
Population: chemicals

Comparator Test





# SWIFT ACTIVE SCREENER



# SWIFT



## ACTIVE SCREENER

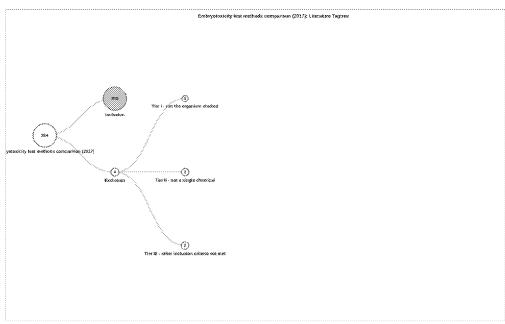
### **Validation: Recall Estimate**

Dataset	WSS Num Obtained Scre		Obtained Recall
transgenerational	0.738	10645	0.957
neuropain	0.626	9254	0.943
bpa	0.65	2688	1
pfos_pfoa	0.619	1815	1
fluoride	0.518	2149	1
statins	0.492	1609	0.959
ace_inhibitors	0.368	1515	0.968
betablockers	0.211	1620	1
opiods	0.174	1569	1
skeletalmusclerelaxants	0.07	1520	1
protonpumpinhibitors	0.375	821	1
calciumchannelblockers	0.469	623	0.989
atypical_antipsychotics	0.241	827	0.992
adhd	0.208	659	1
triptans	0.195	525	1
oralhypoglycemics	0.151	390	0.957
nsaids	0.374	234	1
estrogens	0.355	225	1
urinaryincontinence	0.247	232	1
antihistamines	0.149	251	1

- Active Screener tells u when to stop screening
- Validated Active Screener results on 20 Datasets previously screened manually
- Purple highlight indicates datasets with ca. 2000 total documents; for these, average WSS obtained is 63%
- Software's recall estimate is conservative. When targeted 95% recall, Actual recall averaged 98.8% across all 20 datasets, with 100% recall for 13/20 datasets



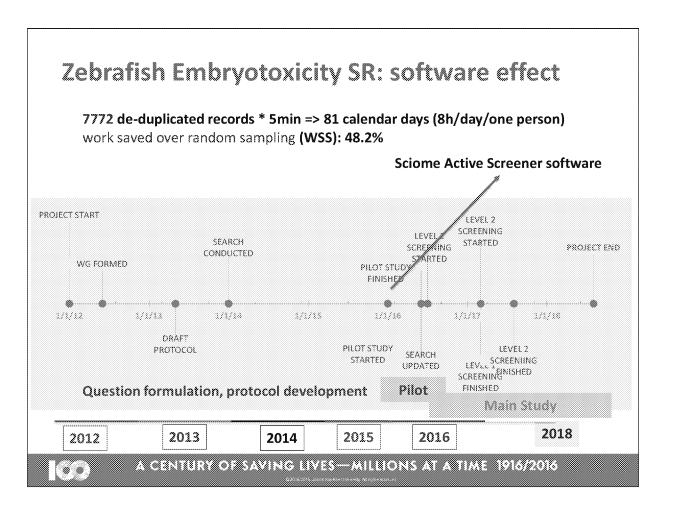
# Data extraction and visualization-HAWC



HAWC visualization generated on October 19 2017, 05:54 PM

https://hawcproject.org/lit/assessment/556/references/visualization/





# EBTC Tox21 study question

Jindex Test

**Main question:** How well do the ToxCast in vitro tests predict the liver outcomes in animal tests (rats, Beagle dogs, non-human primates) and humans?

Comparator tests

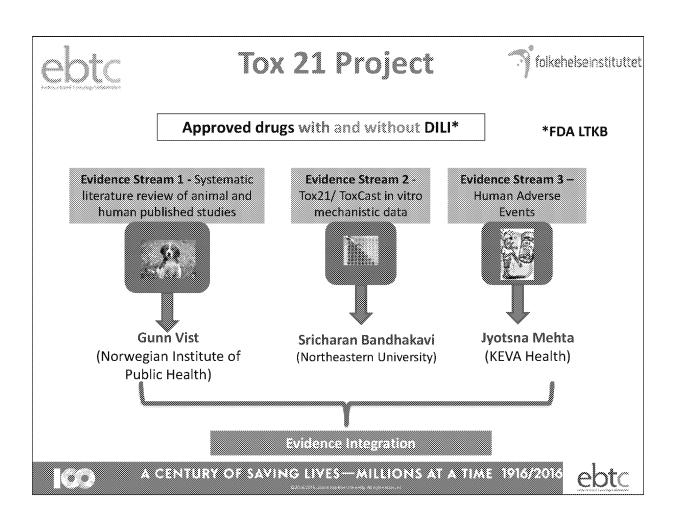
Use a data set from drugs from the Safer Medicines / US EPA ToxCast study

Exposure



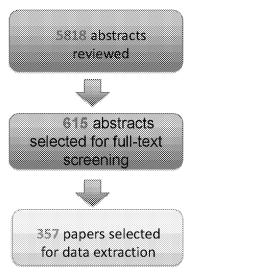






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# Stream 1 - Systematic literature review of adverse effects in experimental animals and humans

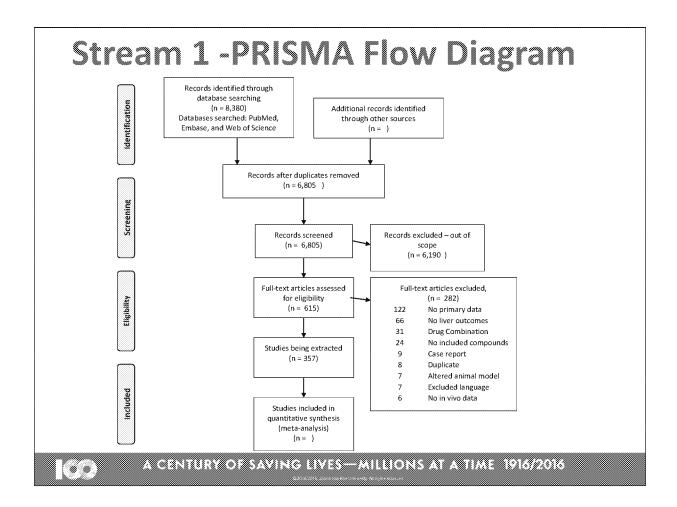


March 31, 2017

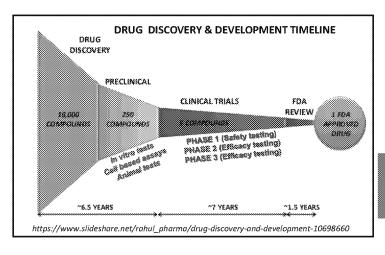
January 11, 2018

March 10, 2018





# How to better leverage preclinical data for eliminating bad drugs from going into clinical trials/market?



#### **EBTC GOAL**

Leverage: SR of literature and Human Adverse Events databases to compare precimical tests performance

#### Tox21 Case study

Comparative analysis of invito, in vitos and adverse events data for two antidiabetic drugs with distinct lives toxicity profiles.



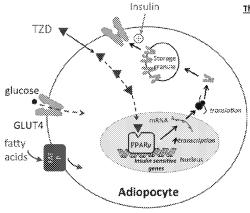
# Drugs pairs case study

Compound 1 Compound 2
(FDA LTKB regulatory Status) Status)

Troglitazone Rosiginazone
Most-DILI-Concern Less-DILI-Concern
withdrawn



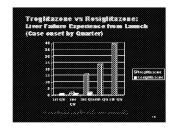
# Anti-diabetic TZD drugs, Troglitazone and Rosiglitazone, stimulate insulin function by targeting PPAR<sub>Y</sub>



 $\underline{http://tmedweb.tulane.edu/pharmwiki/doku.php/thiazolidinediones\ \&\ \underline{www.diabetesincontrol.com}\ (Handbook\ of\ Diabetes,\ 4^{th}\ edition\ excerpt)$ 

#### Thiazolidinediones (TZDs):

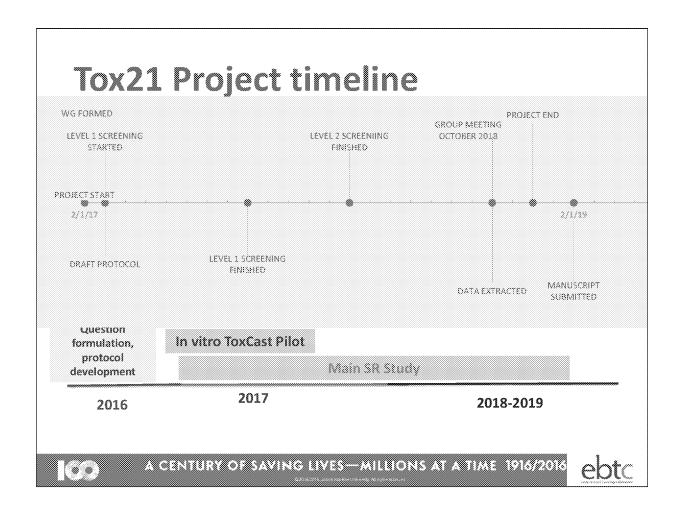
(In market since 1999) Rosigitazone (maleate) – Target: PPARy (withdrawn in year 2000) Traglitazone – Target: PPARy > PPARa



https://www.fda.gov/ohrms/dockets/ac/00/slides/3615s1a/sld018.htm

Can we leverage preclinical data (cell-based assays/test results) for Troulitazone to understand potential basis for toxicity or nonspecificity?







#### Agenda: EBTC Tox21 Stakeholder Input meeting

Dete: October 25, 2018

Location: Fondation pour la Recherche sur la Biodiversité: 195, rue Saint-Jacques , 75005 Paris, FRANCE

Nearest hotel: http://www.hotelpsylussac.com/sn/ Meeting is invitation-only and is limited to 25 participants.

#### PROGRAM

8/30 Registration, Coffee

9:00 am - Hubert Dirven (Norwegian Institute of Public Health) and Katya Tsaloun (EBTC at Johns Hopkins Bloomberg School of Public Health) Welcome and project overview

9:20 - Current practices in in vitra and in silico test methods validation Patience Browne (OSCD)

9:40 - Introduction to Systematic Review as a tool for providing

comprehensive evidence to inform regulatory decisions. Kris Thayer (US EPA) 10:00 Weight of evidence as an integration tool - addressing the new challenges of bridging experimental toxicology, human epidemiological and mechanistic data - Laura Martina (EFSA)

10:20 - Adverse Outcome Pathways as a potential integration tool - Kate Willett (The Humane Society US)

10:20 - coffee break

10:40-12:00 - State of play for each evidence stream - delivered by stream leaders:

10:30 - Evidence stream 1 - Systematic review of animal and human evidence summary and challenges Gunn Vist (Norwegian Institute of Public Health)

11:00 - Evidence stream 2 - ToxCast data analysis results - Sricharan

Blandhakavi (Sri) (Northeastern University)

11:30 - Evidence stream 3 - Real world evidence (RWE) (Jyatana Mehta (KEVA Healthij

12:00 - 1:00 Pm - Lanch

1:00 PM - Introduction to breskout groups work Katya/Hubert

1:30-3:00 pm - Breskaut group work

Feaus: test methods and their ability to best inform decisions. Real project data will be provided 2 weeks before the meeting

1. group It animal data vs. In vitro ToxCast data (moderators confirmed Patience Browne (OECD), and Rob de Vries, SYRCLE) reporteur. |

6/2016



## Obstacles to implementation of EBT

- Duration and expense:
  - Process takes ~2 years and requires expensive reviewers to manually review papers
- Preclinical literature reporting quality:
  - · Missing data
  - · Incomplete methodologies
  - Lack of mature toxicology MeSH tree
- Lack of consistent terminology in outcomes reporting
  - Lack of agreement on ontologies (in vitro and newer models such as zebrafish)
- Variety of study designs
- Lack of established methodologies to assess such study quality and risk of bias



## Primary research issues

#### · Preclinical research quality:

- Incomplete data reporting (e.g., accounting for missing animals)
- · Incomplete methods reporting
- Lack of standardization in many models or outcomes (e.g., histopathology scoring)
- · Lack of power calculation
- No requirement to publish the research protocol
- Duplication of studies

#### Publish or perish:

• One study published in multiple papers

#### Reporting structure:

Lack of structured abstract with key elements of the study reported



## **Example Challenge: Publication standards**

#### Clinical research:

Bhiertine To determine the effectiveness of leveres in the florence technique message thereous and advance from a doctor to take exercise (exercise prescription) along with nurse delivered behavioural counselling for patients with chronic or requirent back pair

Design Enclosis/ randomised trial.

Setting 64 general practices in England.

of these groups were randomised to exercise prescription.

days in pain.

Results Exercise and lessons in the Alexander technique, but not massage, < A R T 1 € L E → 1 N € Q Unempared with control Poland disability score 8.1 massage -0.58, 93% conf Article history: Research -1.40, -2.77 to -0.03, 24 lessons -0.4, -4.76 to -2.83, and exercise. Received 5 April 2013. Research Super 2011

Research

Conclusions One to one lessons in the Alexander technique from registered Gene expression for patients, with chronic back pain. Ser lessons followed by exemple, present Clyrick ether from the control of the Control o

Trial registration National Research Register NOC28106728.

#### Toxicology:

Chemical class-specific gene expression changes in the zebrafish embryo after Participants 579 patients with chronic or recurrent low back pain. 144 were exposure to glycol ether alkoxy acids and 1,2,4-triazole antifungals to missage, 144 to sk Alexander tecmique lessons, and 144 to 24 Alexander.

Sanne A.B. Hermsen \* C.d.\*, Tessa E. Pronk \* C. Evert-Jan van den Brandhofb, berventions brande care from vilk, sie sensions of massage, sie of 24 bessor in the proposition of the sensions of massage, sie of 24 bessor in the proposition of the sensions of massage, sie of 24 bessor in the proposition of the sensions of massage, sie of 24 bessor in the proposition of the sensions of massage, sie of 24 bessor in the proposition of the sensions of massage, sie of 24 bessor in the proposition of the sensions of massage, sie of 24 bessor in the proposition of the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage, sie of 24 bessor in the sensions of massage in the sensio

Instrumentations in the control of t

The zelositish embryodoxiosy best (ZEY) is an afternative test to predict embryodoxiosy of satistances based on two-phological assessment, implementing transcriptoroms; may increase sensitivity and objectivity of the test system. We applied the cheeping approach to compare effects of compounds from two chemical closes, the glycol eithers and 1.2.4 Attaceles, on the embryo, Att 41 byook fertilication, inscriptoray analysis revealed several thousands of responsive genes after glycol either exposure, whereas the trialess significantly regulated per chemical class demonstrated that the ten classes can be distinguished. Gene set enrichment analysis showed that after glycol either exposure mainty gene sets related to development were downer-guisted. More trained exposure, gene sets corresponding to previously described mechanisms of action, such as glycolysis and failty axis metabolism were regulated. Our residire demonstrated that transcriptomics in the EET provides a most resonance englished. Our residire feministrate that transcriptomics in the EET provides a most extensive engineer than standard morphological ascersment. In addition, information about mechanisms of action of substances may become available, thereby facultating the extrapolation of findings to mainmalian species including main.

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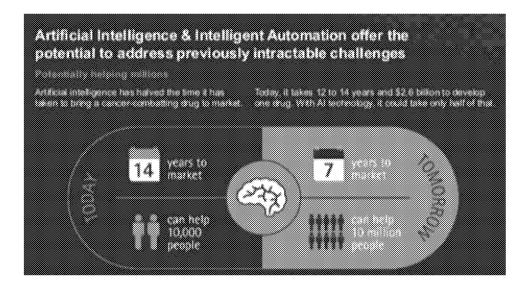


## What funding agencies can do

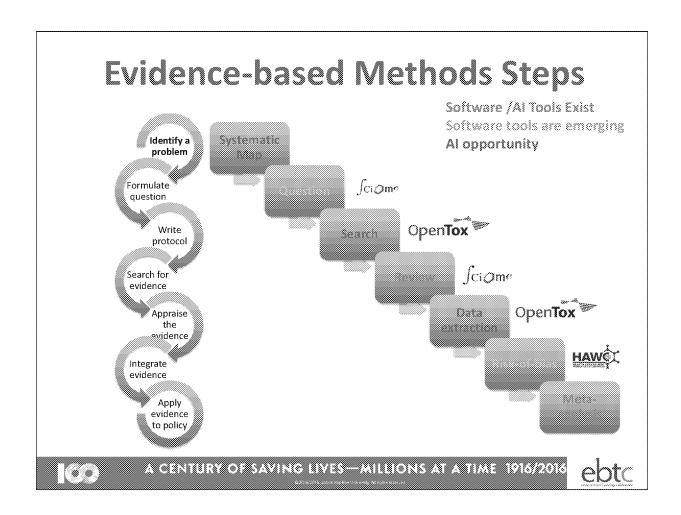
- Demand transparency from the grantees:
  - Require pre-publishing research protocols
    - Fund development of infrastructure
  - Require reporting all data collected (e.g., individual animal data)
- Ensure the study is adequately powered:
  - · Require power calculation
- Require the proper literature search to demonstrate the need for the proposed research (e.g., systematic map)
  - Funding and time should be allowed for this work
- Establish funding mechanisms for translational, cross-discipline and systematic reviews it is systematically underfunded



# Can Al help?



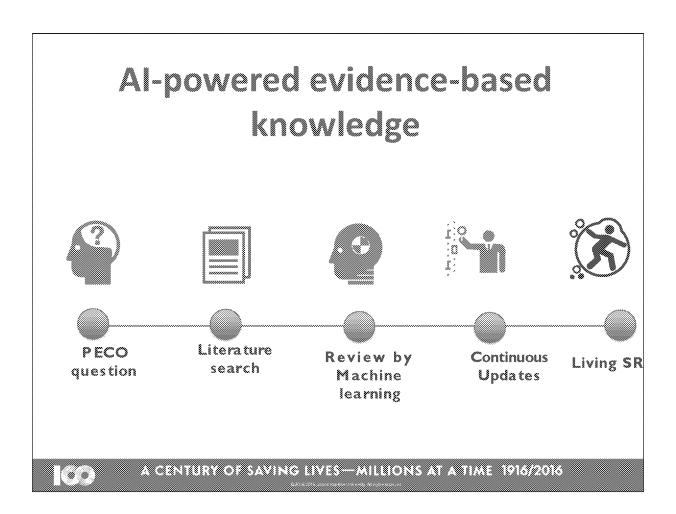




## In ... years we should be able to

- 1. Enter PECO question into an Al-powered browser
- 2. Receive the literature summary and meta-analysis in real time
- 3. Al-powered continuous update of the data a living Systematic Review





### How do we get there? Next steps

- Systematic maps project (graph database technology-based) collaboration with Lancaster University
- Establishing a framework for evidence integration (stakeholder meeting October 25)
- Develop and validate Critical Appraisal Tool for in vitro studies (protocol approved, search executed and is conducted by NIEHS)
- Work with journal editors to establish criteria for structured abstracts in non-clinical literature (Tox journal editors workshop at RTP, Durham, NC May 29-31 2019)
- Working with NLM on developing Toxcology Search Terms (ToSH Terms) to complement MeSH terms to facilitate literature searches





### What are systematic maps?

- Objective is to develop a new approach to providing broad summaries of the characteristics of a large body of research which is relevant to informing a risk management decision
- Systematic reviews synthesise a relatively small number of studies to determine what is already known in answer to a focused research question
- But decisions about what to systematically review, to be evidence-based, require an understanding of the overall geography of the evidence in a topic area: where are the gaps and where are the gluts?
- Systematic maps are an essential prior step in efficiently allocating research capacity for providing relevant evidence to decision-making processes



## Acknowledgements

### **EBTC** staff:

- Martin Stephens, Founding Director of EBTC
- Sebastian Hoffmann, SEH Consulting
- Paul Whaley, University of Lancaster
- Rob de Vries, SYRCLE

**EBTC Board of Trustees** 

**EBTC Scientific Advisory Council** 

**EBTC Zebrafish Working Group** 

**EBTC Tox21 Working Group** 

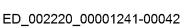


- Sri Bandhakavi
- Nia Peace









### Get in touch

Questions?

ktsaiou1@jhu.edu

+1-410-456-2032



## EBTC Tox21 study question

, Index Test

**Main question:** How well do the <u>ToxCast in vitro tests</u> predict the liver outcomes in <u>animal tests</u> (rats, Beagle dogs, non-human primates) and humans?

Comparator tests

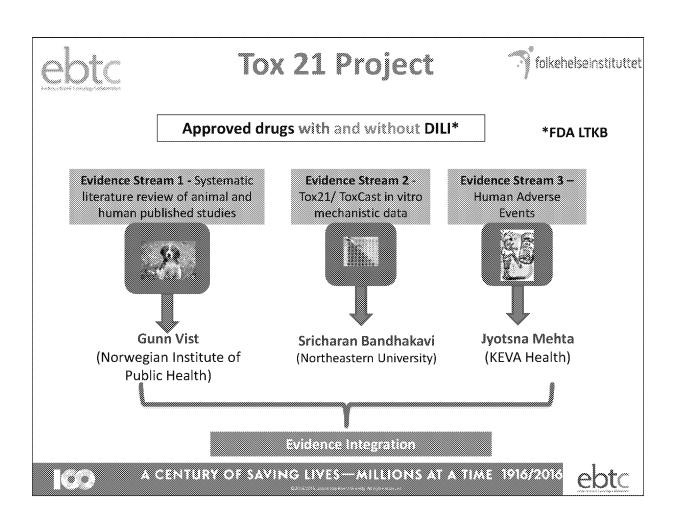
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Exposure



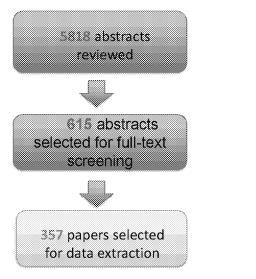






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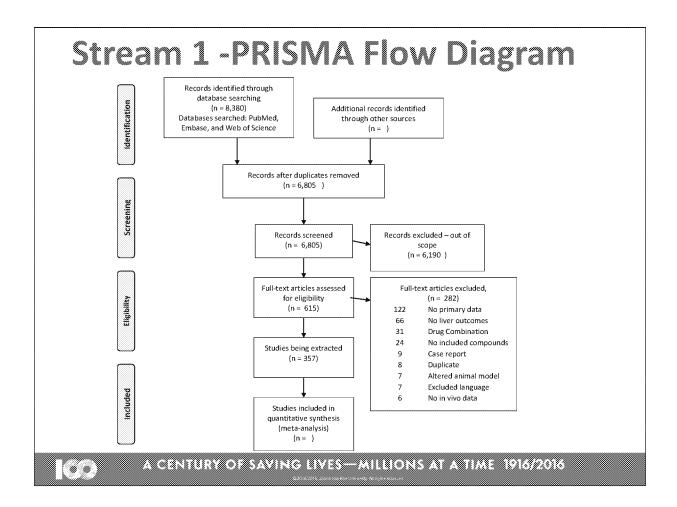


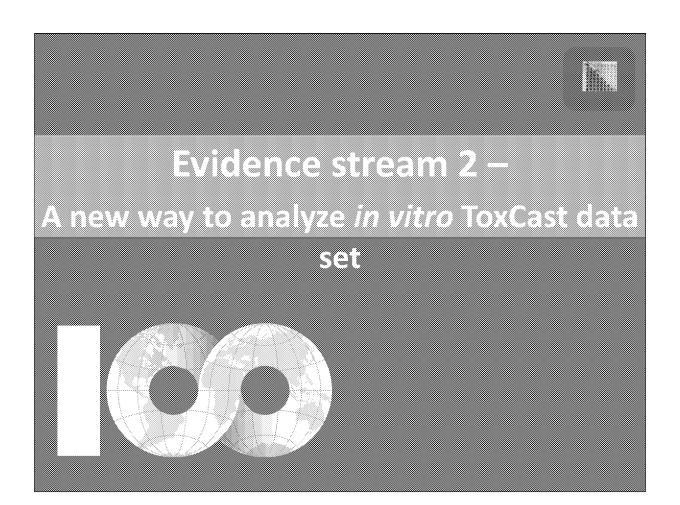
March 31, 2017

January 11, 2018

March 10, 2018







## High level project workflow



Genn/Extract conducting the four IDA2 of debates the two of pass of interest.



From up to 700 cell based as ays/tests, classify all "positive" test results

- Positive with Troglitazone only
- Positive with both Troglitazone and Rosiglitazone Maleate
  Positive with Rosiglitazone Maleate only



- Catalog biological processes affected & their protein targets/families for each drug
   Stratify protein targets/drug based on potential for activation in patients
- Highlight stratified non-specific protein targets for each drug



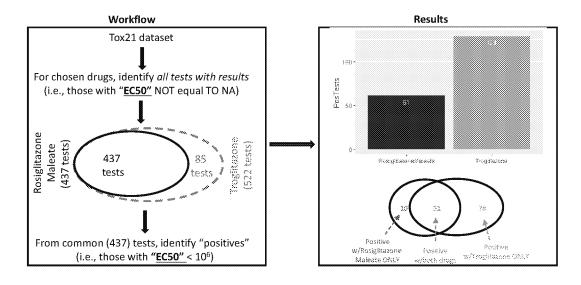
Potential <u>in fatore</u> to further evaluate linkage between stratified non-specific target, and liverspecific side effects, profile of either drug

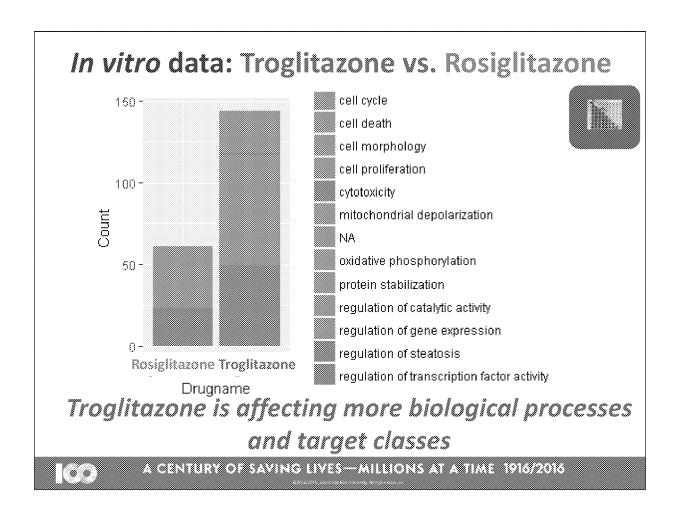


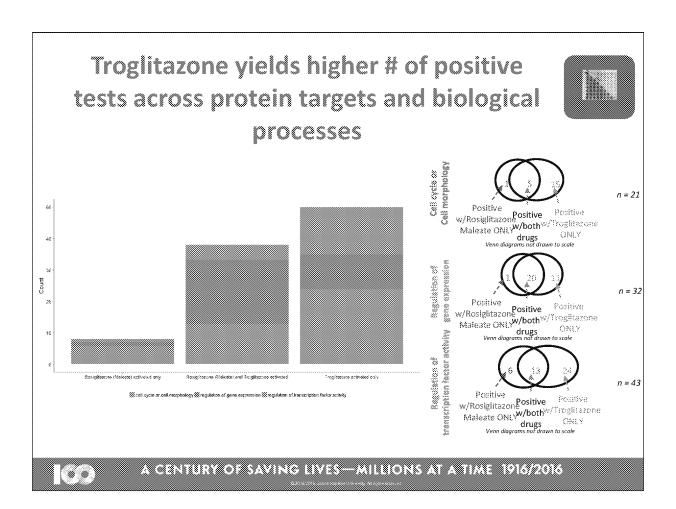




## Higher # of "positive" tests for Troglitazone relative to Rosiglitazone

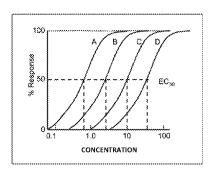


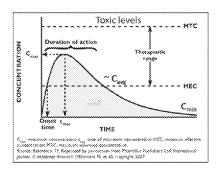




## Stratification of targets' activation potential in humans using Normalized Activation Score







Potency: Drug A > Drug B > Drug C > Drug D

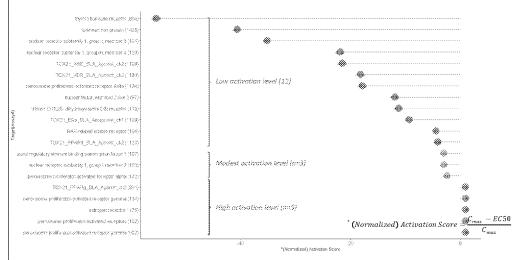
Cmax is closest to toxic levels of drug

- If  $C_{max}$  (of drug in humans) is > EC50 (for any in vitro/cellular assay) higher potential for activation;
- If  $C_{max}$  << EC50, lower potential for activation \* (Normalized) Activation Score =  $\frac{C_{max} EC50}{C_{max}}$



# Potential non-specific transcriptional regulator activations/level by Rosiglitazone in patients



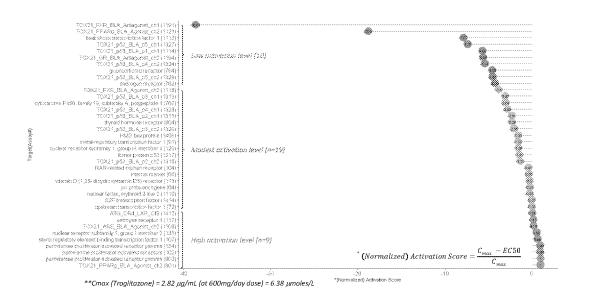


\*\*Cmax (Rosiglitazone Maleate) = 598 ng/mL (at 8mg/day dose) = 1.34 μmoles/L

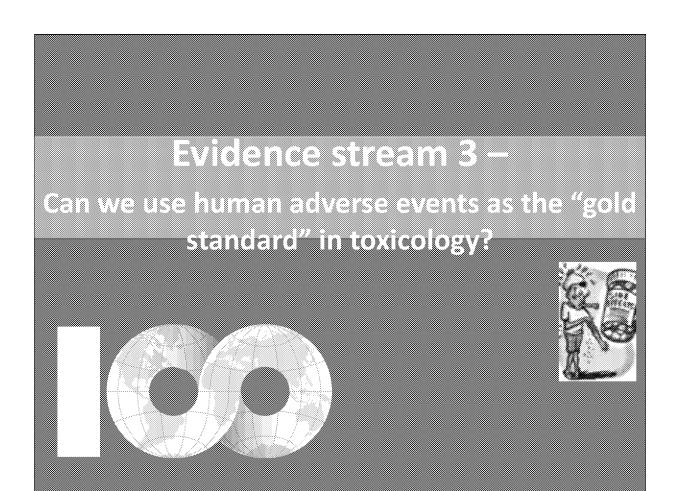


# Potential non-specific transcriptional regulator activations/level by Troglitazone in patients









### WHO Vigibase Data Analysis



#### **€**10 €2

- To provide analysis related to Tox 21 Evidence Stream 3 Human Adverse Events
- Focusing specifically on liver related adverse events for the following drugs:
  - 0.000

#### **About VigiBase**

**VigiBase is the unique WHO global database** of individual case safety reports (ICSRs). It is the largest database of its kind in the world, with over 16 million reports of suspected adverse effects of medicines, submitted, since 1968, by member countries of the WHO Programme for International Drug Monitoring. It is continuously updated with incoming reports.

Data provided for analysis:

Troglitazone Data Rosiglitazone Data (VigiBase)

Created By:

Abhishek Garg Jyotsna Mehta(Mentor)



## Analysis Areas



### Focus of Analysis:

- Comparisons of frequencies of 'Liver Related' Adverse Events vs. 'Other' Adverse Events
  - Specific Health Outcomes / (according to MedDRA codes)
  - - Dose analyses
    - Demographics and Gender



#### **Troglitazone:** Liver Related Adverse Event frequency Tragiitazane: Liver Related Adverse Events Frequency Total Records: 8408 V Liver Related Distinct Reports: 1646 Other Liver Related Reports: 3059 Other Reports: 5349 This Peport provides the trequency of Liver Paletad Adverse : Reported Term Live : Hepatocellular dam. Related : Hopatic failure **495** ^ ₩ 406 Adverse Events across all **⊗** 344 Heastic function st. Jeundine Henatins nos Liver function rests \$ 205 \$ 153 \$ ₩ 313 Exemple: Repetic Fallure was reparted in \* 131 \* 131 Repatit diritoria Blimbin increased Aspartate aminotra. 26% of the roses. Diver injury was reported in 14% of the roses. \* 72 \* 54 \* Aspertent attenders. Liver facts Hapatumagaly Hapatumagaly Hapatumase Cholestillaris Hypertension portal Hapatumagaly Hapatumagaly Hapatumagaly Hapatumagaly Hapatumagaly Hapatumagaly Hapatumagaly Hapatumagaly Hapatumagaly exert apparent of cases reported 846 associated to that particular Adverse Event ∘ 35 AGG(Report ID) Jaunniline chniestatus - 26 0 100 0 200 0 300 0 400 495 Repatitis Repatit neoplasmin Repaturenal syndro... - 15 Cholestrasis intrahed Henstilto a antilhody. Galiolaszar disordar Obslecystitis Hepototosisty

A CENTURY OF SAVING LIVES - MILLIONS AT A TIME 1916/2016

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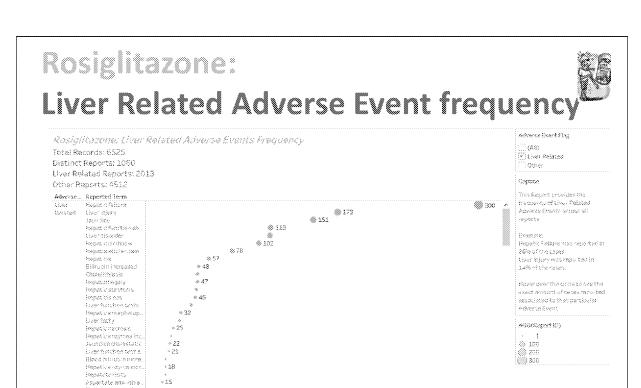
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### Limitations

- Systematic literature review:
  - Publication bias
  - · Lack of regulatory animal tox studies
  - · Positive results bias
  - Reporting deficiencies
- EPA ToxCast:
  - Limited set of assays selected ~ 2005
  - Varied EC50 calculation algorithms (may need to use primary data)
  - Not all drugs tested in all assays
- Vigibase:
  - Not randomized studies
  - No direct data on the number of prescriptions
  - · Reporting incompleteness and potential biases





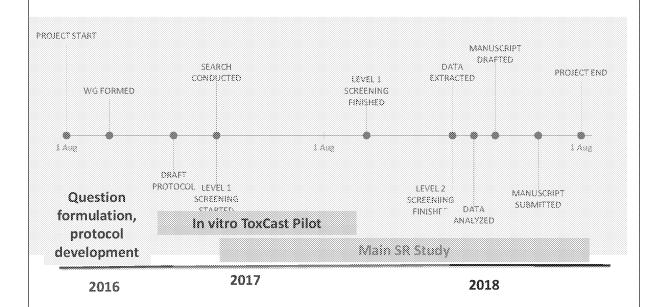
## Challenges

- SR:
  - Manual process to search, review and extract data
- Develop a way to extract and connect diverse outcome measures, e.g.:
  - In vitro: AC50 or point-of-departure
  - Animal: LOAELs, NOAELs (animal), biomarkers of organ toxicity, -omics
  - Human: Biomarkers of organ toxicity, -omics, AE frequencies (human pharmacovigilance, other epi-observational studies), MedDRA terms, Diagosis codes, Adverse Events in clinical trials (human RCTs)
- Connect these outcomes to AOP (or create a systematic map to assemble into a systematic AOP?)











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